DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/25/2008 has been entered.

Claims 1-55 are pending and under examination.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-4, 12-17, 19-25, 32-46, 48-50, 54, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah (U.S. Patent No. 6,020,004, of record), in view of both Chen et al. (U.S. Patent No. 6,537,813, of record) and Tice et al. (U.S. Patent 4,389,330, of record).

Shah teaches a continuous process for the preparation of 0.5 μ microparticles for nucleic acid delivery, the process comprising obtaining a first emulsion by mixing, in a homogenizer, PLGA dissolved in an organic solvent with a first aqueous solution of a nucleic acid, and mixing the first emulsion with a second aqueous solution comprising a surfactant, and a stabilizer comprising sucrose and a buffer such as Tris-HCl (i.e., both the first emulsion and the first aqueous solution comprise a stabilizer), and further mixing this combination to form a second emulsion, then transferring the second emulsion to a lyophilizer to remove the solvents (claims 1, 3, 17, 32-36, 41, 42, 48, and 50) (column 4, lines 25-65, column 5, lines 50-62, column 6, lines 5-45, column 7, lines 30-40, Example 1). Shah also teaches that the organic solvent comprises methylene chloride (i.e., dichloromethane) (claim 25) and that the second aqueous solution can comprise polyvinyl alcohol (claim 40) (column 6, lines 5-7, Example 1). Shah does not teach a scalable continuous process (claim 1). Chen et al. teach a scaleable, concurrent flow mixing method and apparatus for the preparation of nucleic acid-containing microparticles, wherein the method comprises concurrently introducing and mixing at least a first molecular entity-containing solution and a second molecular entity-containing solution into a flow through mixer (i.e., mixer chamber) to form an uniform microparticle suspension, collecting the suspension in vessels attached to the apparatus, and storing the microparticles in solution or in more concentrated forms, including lyophilized particles (column 1, lines 15-22, column 3 bridging column 4, column 19, lines 50-60). Chen et al. teach that their method and apparatus can be adapted for (i) the mixing of more than two solution, wherein the mixing of the first

components takes place before the introduction of the additional solutions (column 9 bridging column 10) and (ii) a continuous process (column 21, lines 47-63). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Shah by using the apparatus of Chen et al., with a reasonable expectation of success. The motivation to do so is provided by Chen et al., who teach that no other mixing format allows for convenient, reliable, reproducible, and scaleable process that results in the production of uniform quality and particle size specific for different applications (column 6, bridging column 7, column 10 bridging column 11). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because Chen et al. teach that their apparatus can be successfully adapted for the preparation of microparticles with diverse composition, according to the needs.

Neither Shah, nor Chen et al. teach removing the organic solvent from the second emulsion to form an aqueous suspension of microcapsules (step "f" of claim 1). Tice et al. teach that removal of the organic solvent in two distinct steps, rather than in one step, results in microcapsules with improved quality and containing a higher level of active agent, wherein the first steps involves techniques common in the art such as evaporation, heating, extraction or vacuum (claims 20-22 and 24) followed by separation of the microcapsules from the fluid medium by filtration through a fine (4-5.5 μm) fritted-glass funnel and removal of the remaining solvent by resuspending the microcapsules in water, wherein the water extracts the solvent from the microcapsules (claim 23). Tice et al. teach that during the second extraction step, the aqueous medium

with the extracted solvent must be removed and replaced with fresh aqueous medium on a continuous basis and that after the remaining of the solvent has been removed, the microcapsules are dried by conventional techniques (column 2, lines 14-29, column 4, lines 9-54, column 6, Example 1). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to further modify the method taught by the combined teachings of Shah and Chen et al. by removing the solvent using the two-step procedure of Tice et al., with a reasonable expectation of success. The motivation to do so is provided by Tice et al., who teach that the two-step procedure results in higher levels of active agent as compared with the conventional one-step procedure. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches this procedure can be successfully used to obtain better quality particles, while preserving the activity of the encapsulated agent.

With respect to the limitations recited in claims 19, 44-46,54, and 55, Chen et al. teach that both the size and uniformity is regulated by controlling the mixing ratio, flow rate, and mixing rate (column 6 bridging column 7). Absent evidence of unexpected results, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation.

With respect to the limitations of the buffer being Tris-EDTA (claims 4 and 49), the first and second solution having the same osmolarity (claim 2), of the wash solution being sterile water at a temperature of about 2°C to about 8°C (claim 14), of adding an

excipient (claim 15), transferring the dried microparticles into one or more vessels (claim 16), of the heating between 30°C and 55°C (claim 21), of the ratio of lactic acid to glycolic acid being between about 1:2 and about 4:1 (claim 37) or about 1:1 (claim 38), of the PLGA having an average molecular weight of 6,000 to 100,000 (claim 39), or of the emulsifying step being carried out between about 2°C to about 8°C (claim 43), absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results. One of skill in the art would have discovered the optimal working conditions by routine experimentation.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that, having read Shah and Tice, one of skill in the art, would not have had any reason to modify the single-step method of Shah to include the multi-step method of Tice.

With respect to Shah, Applicant argues that the reference describes "an improved method for preparing polymeric microparticles containing an active ingredient through unique utilization of direct lyophilization of emulsion or suspension" (column 2, lines 56-59); the "direct lyophilization" methodology is used to remove aqueous and organic solvents and produce the microparticles (column 5, lines 63-65). According to Shah "[i]t is utilization of this single step, i.e., direct lyophilization of the final emulsion or

suspension, which refines and simplifies the present process over previously described processes, which require multiple steps and are often cumbersome" (column 6, line 66, to column 7, line 3). Shah places a clear emphasis on the importance of using only a single step (direct lyophilization) on the final emulsion or suspension. Applicant points out that The Background section of Shah refers to the same Tice reference (i.e., U.S. Pat. No. 4,389,330) cited in the present Office Action. In its reference to Tice, Shah states that the solvent evaporation technique (as described in Tice) "is often not preferred because active ingredient is often lost during the solvent extraction process" (column 2, lines 11-12). In summarizing the importance of direct lyophilization to his methods, Shah states that his one-step method "provides several significant advantages over the processes described in the art", which include ease of manufacture, provision of sustained release formulations which maintain the activity and integrity of the active ingredient during release, and attainment of higher yields, and higher loading efficiencies (column 2, line 56, to column 3, line 5 and 13-16). According to Applicant, Shah's comments on the advantages of the single-step direct lyophilization method as compared to the multi-step solvent evaporation process of Tice directly contradict the remarks in the Office Action alleging that Tice's methods achieve "higher active agent loading and microparticles quality" and that "one of skill in the art would have been motivated to sacrifice simplicity for quality, in order to achieve microparticles with superior characteristics." Applicant submits that Shah teaches the method as superior to those in the art. In view of the teachings of Shah and Shah's direct commentary on Tice (which published about 14 years before the filing date of Shah),

one of skill in the art would have been strongly discouraged from modifying Shah' method by adding Tice's two-step solvent removal method. Applicant submits that Shah teaches that such a modification would have been expected to result in both a more cumbersome method as well as the production of a lower quality product, i.e., Shah teaches away from the claimed invention. As a result, Applicant argues, the combination of Shah, Chen, and Tice does not render the claimed invention obvious and the rejection should be withdrawn.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Applicant argues that Shah teaches away from the claimed invention because Shah discourages using Tice's two-step solvent removal method. In response to this argument, it is noted that MPEP clearly states that a teaching away from the invention is a teaching which renders prior art unsatisfactory for the intended purpose (MPEP 2145 [R-6] X D). However, Shah does not discourage from using Tice's method because Shah clearly teaches that Tice's method is useful in certain instances, i.e., the method is satisfactory for the intended purpose (column 2, lines 6-10). Shah only teaches that Tice's method is not preferred for water-soluble drugs because such drugs could be lost via partition into the aqueous solution (column 2, lines 11-16); however, such does not constitute a teaching away because it does not criticize Tice's method. In fact, as noted above, Shah does teach that Tice's method is useful when used with drugs which do not easily partition into the aqueous phase. It is noted that the instant case pertains to nucleic acids and not to water-soluble drugs. One of skill in the art would not expect

that nucleic acids would be lost by partition because nucleic acids are condensed by and form complexes with the polymers used to encapsulate them. Therefore, by reading Shah, one of skill in the art would not recognize that the teaching of "not preferred" would apply to nucleic acids. With respect to Tice, the reference clearly teaches that the two-step solvent removal method achieves unexpectedly higher active agent loading and microparticles quality than the single-step methods. Such teachings, would motivate one of skill in the art to sacrifice simplicity for quality, i.e., to modify Shah's method by using the Tice's two-step solvent removal method. For all the reasons above, the rejection is maintained.

4. Claims 1-6, 12-17, 19-25, 32-46, 48-50, 54, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah taken with Chen et al. and Tice et al., in further view of Parikh et al. (U.S. Patent No. 5,660,858, of record).

The teachings of Shah, Chen et al., and Tice et al. are applied as above for claims 1-4, 12-17, 19-25, 32-46, 48-50, 54, and 55. Shah, Chen et al., and Tice et al. do not teach a lipid as a stabilizer (claims 5 and 6). Parikh et al. teach using lipids as stabilizers. It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Shah taken with Chen et al. and Tice et al. by including lipid stabilizers, with a reasonable expectation of success. The motivation to do so is provided by Parikh et al., who teach that the use of lipids results in increased stability during diverse processing steps, such as heating or storage, and also under

stress conditions, such as shaking, vibrating, and termal cycling (column 3, lines 2-6). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that lipids can be successfully incorporated into microparticles. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that Parikh et al. do not remedy the deficiencies noted above.

Applicant's argument is acknowledged however, the rejection is maintained for the reasons set forth above.

5. Claims 1-4 and 7-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah taken with Chen et al. and Tice et al., as applied to claims 1-4, 12-17, 19-25, and 32-46 above, in further view of both Hartounian et al. (PGPUB 2002/0039596, of record) and Hedley et al. (U.S. Patent 5,783,567, of record).

The teachings of Shah, Chen et al., and Tice et al. are applied as above for claims 1-4, 12-17, 19-25, 32-46, 48-50, 54, and 55. Shah taken with Chen et al. and Tice et al. do not teach a diafiltration apparatus or a hardening tank (claims 7-11, 18, 26-28, and 47). Hartounian et al. teach aseptical preparation of liposomes using a diafiltration apparatus such as a hollow fiber filter or a hardening tank (p. 2, paragraphs 0020 and 0021, p. 4, paragraph 0062, p. 5, paragraphs 0063-0066, p. 8, paragraphs

0104-0107, p. 9, paragraphs 0112, p. 10, paragraph 0126). It would have been obvious to one of skill in the art, at the time the invention was made, to optimize the production process by employing diafiltration apparatuses, as taught by Hartounian et al. One of ordinary skill in the art would have been motivated to do so in order to enhance the production of large quantities of microparticles for use in the delivery of nucleic acids and to reduce the time in preparing the desired amount of particles. Since the totality of the prior art of record teaches that the microparticles are for *in vivo* use, one of ordinary skill in the art would have been motivated to ensure that all of the components used in the making of the microparticles are sterile, so as to ensure that sterility is preserved throughout the process. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that such methods can be successfully practiced. With respect to the different residual organic solvent levels recited in claims 10 and 11, Shah teaches that the removal of organic solvent during lyophilization can be monitored (Example 1); therefore, one of skill in the art would only require routine experimentation to achieve and determine these levels. With respect to the limitations of the nucleic acid being in the form of circular RNA or supercoiled DNA (claims 29-31 and 51-53), one of ordinary skill in the art would have expected that either circular RNA or supercoiled DNA molecules are present in the microparticles, because the conditions of encapsulating nucleic acids within microparticles without destroying their structure, thereby allowing for the intracellular delivery of functional RNA or DNA via microparticles, were routine at the time the invention was made, (see Hedley et al., Abstract, column 1, lines 30-58). Thus, the

claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that Hartounian et al. and Hedley et al. do not remedy the deficiencies noted above.

Applicant's argument is acknowledged however, the rejection is maintained for the reasons set forth above.

Conclusion

6. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Examiner, Art Unit 1633